The Metabolic Syndrome Update
2013

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The Metabolic Syndrome: Overview

- What is it?
- Why do we care?
- How do we define it?
- How should we manage it?
- Is there a controversy?

Global Cardiometabolic Risk

- Smoking
- LDL-HDL
- HTN
- Age
- Sex
- Family
- Diabetes

- Inflammation
- Obesity
- Triglycerides
- Insulin Resistance
- Thrombosis
The Metabolic Syndrome:
General “Clustering” of Features

• Abdominal obesity
• Atherogenic dyslipidemia
  – Elevated Triglycerides
  – Low HDL-Cholesterol
  – Small dense LDL particles
• Raised blood pressure → HTN
• Insulin resistance → IFG, IGT, GDM, T2DM
• Prothrombotic state
• Proinflammatory state
• Non-Alcoholic Fatty liver disease
• Others?

The Metabolic Syndrome:
A Little History

• HTN-Hyperglycemia-Gout - Kylin 1923
• Insulin Insensitivity - Himsworth 1936
• “Diabetogenic Obesity” - Vague 1947
• “Syndrome X” – Reaven 1988
• WHO - Metabolic Syndrome 1998
• NCEP - Metabolic Syndrome 2001
• Dysmetabolic Syndrome (277.7) 2003

Consensus Definition:
The Metabolic Syndrome

Diagnosis Established When ≥ 3 are Present:
• Elevated Waist Circumference
  – Men: > 40 in; Women: > 35 in
  – Population and country specific
• Elevated Triglycerides: ≥ 150 mg/dl*
• Low HDL Cholesterol*
  – Men: < 40 mg/dl
  – Women: < 50 mg/dl
• Elevated Blood Pressure: ≥ 130/85*
• Elevated Fasting Glucose: ≥ 100 mg/dl*
### Population Specific Waist Circumference Thresholds

<table>
<thead>
<tr>
<th>Population</th>
<th>Waist Circumference (cm)</th>
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<tbody>
<tr>
<td></td>
<td>Men</td>
</tr>
<tr>
<td>Caucasian</td>
<td>102</td>
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<tr>
<td>Asian</td>
<td>90</td>
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<tr>
<td>Middle East</td>
<td>94</td>
</tr>
<tr>
<td>Sub-Saharan African</td>
<td>94</td>
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<tr>
<td>Central/South America</td>
<td>90</td>
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</tbody>
</table>

### Problems With the Definitions

- Should all factors be given the same weight?
- Who measures waist circumference?
- Is Impaired Fasting Glucose even at the 100 mg/dl cutoff sensitive enough? And now should we be using the A1c ($\geq 5.7\%$)?
- What about “treated” risk factors, should they still count?

### And So Why Should We Care About The Metabolic Syndrome?
Abdominal Adiposity as a Component of Cardiometabolic Risk

Diabetes Prevention Program Progression to Diabetes

The Metabolic Syndrome Type 2 Diabetes Incidence
**Association of the Metabolic Syndrome with CHD**

![Bar chart showing prevalence of CHD associated with different glucose tolerance levels and metabolic syndrome presence.]

**Metabolic Syndrome and Cardiovascular Disease Mortality**

Middle-Aged Men – Median Follow Up 11.6 y

![Bar chart showing relative risk of mortality associated with metabolic syndrome and cardiovascular disease.]

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**The Metabolic Syndrome CVD Risk**

- *Is the* CVD risk of the syndrome greater than the sum of its parts?
- Does the presence of the Metabolic Syndrome predict CVD incidence better than already established risk assessments?
- Does it matter?
Factors Supporting the Metabolic Syndrome as a CVD Risk Factor

- It is accepted and well established that multiple risk factors confer greater risk.
- Majority of studies show the MetS to be an independent predictor of CVD risk.
- A recent meta-analysis found that the risk for CVD is still increased in people with the MetS (RR, 1.54), even after controlling for the component risk factors\(^1\).
- Post hoc analysis of 4S and AFCAPS/TexCAPS showed that individuals with the MetS had increased risk for major coronary events irrespective of their FRS\(^2\).


The Metabolic Syndrome
Other Associated Conditions

- Nonalcoholic Fatty Liver Disease
- OSA
- PCOS
- Hypogonadism
- Lipodystrophies
- Microvascular Disease
- Others

Is There a Unifying Pathophysiologic Cause of the Metabolic Syndrome?

- Maybe – Maybe Not
- Abdominal adiposity and Insulin Resistance appear to be at core of pathophysiology of the Metabolic Syndrome AND its individual components
- Targeting visceral adiposity and insulin resistance should be central to the management of the Metabolic Syndrome patient
- All of the components of the Metabolic Syndrome improved when adiposity and insulin resistance are targeted
The Consequences of the Metabolic Syndrome

- Obesity
- Hyperinsulinemia
- Insulin Resistance
- Diabetes
- Dyslipidemia
- ↑ Thrombosis
- Hypertension
- Repro-Endo NAFLD
- Macrovascular Disease

Obesity and Insulin Resistance

- Classic Pathophysiology
  - ‘Portal’ Hypothesis
  - ‘Primary’ defect in insulin signaling in skeletal muscle and adipose tissue
- "New" Ideas in the Pathophysiology
  - Inadequate number of fat cells relative to the energy ‘burden’, i.e. failure of the adipose organ, resulting in ectopic fat deposition and lipotoxicity
  - Adipocytokines and Inflammation

Adipose Tissue:
Storage Function

- TG → FFA
Adipose Tissue: Secretory Function

**Adipo- or Lipocytokines**

- Leptin
- IL-6
- Angiotensin
- Others
- TNF-α
- PAI-1
- Resistin
- Adipsin
- Adiponectin

**Adipocytokines**

- TNF-α
- IL-6, IL-8
- MCP-1
- TGF-β
- FGF
- EGF
- Fatty acids
- Lysophospholipid
- Lactate
- Adenosine
- Prostaglandins
- Glutamine
- Estrogen
- Bone Morphogenic Protein
- IGF-1
- IGF-BP
- Angiotensin II
- Adipsin
- Resistin
- Viscatin
- Glucagon
- Adenine
- Prothrombotic state
- Adiponectin
- Acylation-Stimulating Protein
- Unknown Factors
- Agouti
- Retinol binding protein
- Plasminogen activator inhibitor -1

**Hypertension**

- FFA
- HDL cholesterol
- Small dense LDL
- VLDL
- CRP
- Glucose
- TNF-α
- IL-6
- VH
- FFA
- Insulin
- IL-6
- VNS
- Glucose
- TNF-α
- IL-6
- FFA
- PAI-1
- Prothrombotic State
- Triglyceride (intramuscular droplet)
- CRP
- Fibrinogen
- Prothrombotic State

**References**

- Pittas AG, J Clin Endocrinol Metab 2004; 89:447-52
- Eckel et al, Lancet, 2005
Visceral Adiposity, Insulin Resistance and the Metabolic Syndrome

- Insulin resistance may or may not be unifying pathophysiologic cause of the Metabolic Syndrome
- Nevertheless, targeting visceral adiposity and insulin resistance should be central to the management of the Metabolic Syndrome patient
- All of the components of the Metabolic Syndrome improved when adiposity and insulin resistance are targeted

Clinical Management of The Metabolic Syndrome

Who Should We Screen for the Metabolic Syndrome?

- If one feature is present look for the others!
- Screen everyone over age 40
- Screen everyone who is obese and/or has elevated waist circumference
- Look for the pattern
How Should We Screen for the Metabolic Syndrome?

- Vital signs
  - blood pressure
  - waist circumference
- Fasting blood work (glucose, lipids)
- Economical
  - cost of vital signs included in clinic visit
  - FLP/BG ~$30
- Easy for patients to understand
- Billable: ICD-9 code 277.7

The Metabolic Syndrome: Treatment Goals

- Obesity
- Hyperinsulinemia
- Insulin Resistance
- Diabetes
- Dyslipidemia
- Thrombosis
- Hypertension
- Repro-Endo
- NAFLD
- Macrovascular Disease

The Metabolic Syndrome: Treatment

- No ‘right answer’ at this time
- Lifestyle Modification: diet and exercise
  - Minimal risk, relatively low cost, proven efficacy
  - Preferred approach especially in low risk individuals?
- Pharmacologic Therapy
  - Be clear in your own mind about what you are treating
  - obesity: weight loss drugs
  - Insulin resistance: metformin, TZDs
  - Dyslipidemia: statins, fibrates, niacin
  - Hypertension: ACE I, ARB
  - Hypercoaguable State: aspirin
So What Should We Do?
*Proposed Clinical Approach to Treating the Metabolic Syndrome Patient*

- Identify At-risk Populations
- Encourage Lifestyle Changes
  - Weight Loss (~5%)  
  - Increased activity
- Improvement
  - and weight, blood pressure, lipids, etc.
- No improvement/worsening
  - Lifestyle changes
  - Wt Loss Agents
  - Metformin
  - TZDs
- Treat other CRFs and Comorbidities

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*The Metabolic Syndrome*

Summary of the Problem

- Very common
- Prevalence is increasing
- Associated with significant comorbidities
  - HTN
  - Dyslipidemia
  - Repro-Endo issues
  - Atherosclerotic Cardiovascular Disease
  - Progression to T2DM
- Many unanswered questions…